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Deciphering *APOE* Gene Interaction Networks in Alzheimer's Disease: A Comprehensive Analysis of Genetic Factors and Their Potential as Therapeutic Targets

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ABSTRACT

Background: Alzheimer's disease (AD) is a prevalent neurodegenerative disorder characterized by progressive cognitive decline. The apolipoprotein E (*APOE*) gene, particularly its ε4 allele, is a well-established genetic risk factor for late-onset AD. This study aimed to decipher APOE's interaction networks to advance AD diagnostics and therapeutics.

Materials and Methods: We conducted an analytical study comparing gene expression data and genetic factors between AD patients and healthy controls. Candidate genes were identified through comprehensive literature reviews and bioinformatics database searches, prioritizing genes validated by in vivo, in vitro, or in silico evidence. Interaction networks were constructed using MATLAB software, version R2025a and R software, version 4.5.1.

Results: Network analysis of AD-associated proteins—using centrality measures (maximum neighborhood component (MNC), degree, betweenness, closeness, and radiality)—identified TREM2, BDNF, NCSRN, SORL1, and TNF as key components within the APOE network. TREM2 and TNF regulate neuroinflammatory responses, BDNF supports neurotrophic activity and synaptic plasticity, NCSRN modulates Notch signaling, and SORL1 is critical for amyloid-beta (Aβ) metabolism. These findings highlight AD's multifactorial nature and reveal potential therapeutic targets and biomarkers.

Conclusion: Our results align with prior research, reinforcing the roles of TREM2 (microglial activity), BDNF (neuroprotection), NCSRN (signaling pathways), and SORL1 (Aβ regulation) in AD pathogenesis. By mapping APOE's interaction network, this study provides a foundation for future therapeutic innovations.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting millions worldwide, characterized by cognitive decline, memory impairment, and behavioral disturbances [1, 2]. With the aging global population, AD has emerged as a critical public health challenge, underscoring the urgent need to elucidate its molecular mechanisms. Despite decades of research, AD's etiology remains complex and multifactorial, involving intricate interactions between genetic predisposition, environmental factors, and pathological processes [3].

AD is broadly classified into early-onset AD (EOAD) and late-onset AD (LOAD) based on age of onset. EOAD manifests before the age of 65 and is frequently linked to autosomal dominant mutations in amyloid precursor protein (APP), Presenilin-1 (PSEN1), and PSEN2 [4, 5]. These mutations disrupt amyloid-beta (Aβ) metabolism, promoting excessive plaque deposition and subsequent neuronal dysfunction [6]. In contrast, LOAD accounts for the majority of cases and typically occurs after the age of 65, arising from complex interactions between genetic susceptibility (e.g. the apolipoprotein E (APOE) ε4 allele) and environmental risk factors. Notably, the APOE ε4 allele represents the strongest genetic risk factor for LOAD, driving pathogenesis through mechanisms, including impaired Aβ clearance, exacerbated neuroinflammation, and synaptic dysfunction [7, 8].

The pathobiology of AD is characterized by hallmark molecular and cellular alterations, including extracellular Aβ plaque deposition, intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein, progressive synaptic dysfunction, mitochondrial dysregulation, oxidative stress, and chronic neuroinflammation, all of which collectively contribute to neurodegeneration and cognitive decline [9, 10]. Aβ, a proteolytic fragment derived from APP processing, progressively accumulates as extracellular plaques that impair neuronal signaling and initiate neurotoxic pathways. These Aβ aggregates disrupt synaptic plasticity while concurrently activating microglia-mediated neuroinflammatory responses, creating a vicious cycle that amplifies neurodegeneration [11-13]. The accumulation of Aβ plaques demonstrates a robust correlation with key pathological hallmarks of AD, including progressive neurodegeneration, synaptic depletion, and measurable cognitive decline. These consistent pathological associations have established dysregulated Aβ metabolism as a pivotal research focus in AD therapeutics and biomarker development [14]. Tau pathology represents a critical component of AD progression, characterized by the accumulation of hyperphosphorylated tau proteins that aggregate into intracellular neurofibrillary tangles. These pathological inclusions disrupt microtubule stability, impair axonal transport mechanisms, and ultimately drive progressive neuronal degeneration and synaptic failure [15, 16]. Under physiological conditions, tau protein maintains microtubule stability and facilitates axonal transport. In AD, however, pathological hyperphosphorylation of tau disrupts its normal function, leading to: (1) decreased microtubule-binding affinity, (2) dissociation from microtubules, and 3) subsequent accumulation of insoluble aggregates within neurons [17]. This pathological cascade severely compromises axonal integrity, ultimately leading to synaptic dysfunction and progressive neurodegeneration. Concurrently, chronic neuroinflammation - mediated by persistently activated microglia and reactive astrocytes - constitutes a central driver of AD pathogenesis. This self-sustaining inflammatory state, perpetuated by pro-inflammatory cytokine cascades and oxidative stress mechanisms, not only exacerbates neuronal loss but also synergistically enhances Aβ toxicity, creating a vicious cycle of disease progression [18, 19]. In AD, microglia - the brain's resident immune cells - undergo pathological overactivation, triggering excessive release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6. This chronic neuroinflammatory response contributes to synaptic dysfunction, promotes neuronal apoptosis, and exacerbates Aβ toxicity, thereby accelerating disease progression [20]. Although neuroinflammation initially serves a neuroprotective function by promoting debris clearance and tissue repair, chronic microglial activation induces a maladaptive cascade characterized by (a) excessive reactive oxygen species production, (b) progressive synaptic impairment, and (c) activation of apoptotic pathways - collectively exacerbating neurodegenerative processes in AD [21]. *APOE* ε4 genotype is associated with amplified neuroinflammatory responses, including elevated pro-inflammatory cytokine production and exaggerated microglial activation, demonstrating a clear genetic predisposition for immune dysregulation in AD pathogenesis [22, 23]. The *APOE* gene, located on chromosome 19, encodes apolipoprotein E, a critical lipid transport protein involved in cholesterol homeostasis and neuronal repair [24]. *APOE* exists in three major allelic forms: ε2, ε3, and ε4, each exerting distinct effects on AD risk. The ε4 allele is the strongest genetic risk factor for LOAD, promoting Aβ aggregation, impairing clearance mechanisms, and intensifying neuroinflammatory responses [25]. *APOE* influences

disease pathology through multiple mechanisms, including Aβ clearance, lipid transport, and synaptic repair, and inflammatory regulation. *APOE* ε4 impairs Aβ clearance, resulting in excessive plaque deposition and neuronal toxicity [26, 27]. Additionally, *APOE* plays a role in brain lipid metabolism, affecting synaptic plasticity and neuroprotection [28]. Finally, *APOE* ε4 is associated with increased neuroinflammation, exacerbating disease progression [29].

Given its critical involvement in AD, deciphering *APOE* interaction networks is essential for understanding disease pathogenesis and identifying potential therapeutic targets. Network-based approaches allow researchers to map gene interactions and pinpoint key regulatory nodes, providing insights into pathways that may be leveraged for intervention [30]. Recent advances in bioinformatics, high-throughput genomic analysis, and computational network modeling have revolutionized our ability to identify *APOE*-associated pathways in AD pathogenesis. The integration of multi-omics data (including transcriptomic and proteomic datasets) has enabled systematic mapping of molecular interactions, revealing novel therapeutic targets and biomarkers.

This study employed an integrative computational approach to: (a) construct a comprehensive *APOE* interaction network, (b) identify critical regulatory hubs through network centrality analysis, and (c) characterize their functional roles in AD progression. By elucidating these complex gene-protein relationships, our findings provide mechanistic insights into *APOE*-mediated pathology, potential diagnostic biomarkers with clinical translation potential, and novel targets for therapeutic intervention. These results significantly advance the framework for precision medicine in AD, offering data-driven strategies for developing targeted therapies against this complex neurodegenerative disorder.

Materials and Methods

Study population and sampling

This analytical study was conducted on gene expression data derived from AD patients and a control group of healthy individuals. The datasets utilized in this research were obtained from established bioinformatics repositories, ensuring the inclusion of validated genetic profiles for comparative analysis.

Data collection and network construction

Gene expression data relevant to AD were systematically retrieved from well-recognized bioinformatics databases, including NCBI, SWISS-Prot, and Diseasome. These repositories provided access to curated gene expression datasets from both AD patients and healthy individuals, serving as the gold standard for identifying disease-associated genetic patterns. The collected data formed the basis for constructing an interaction network, enabling the exploration of gene-to-gene relationships within AD pathology.

Gene selection and expression data extraction

Candidate genes implicated in AD were identified through a multi-tiered approach that combined literature reviews and bioinformatics database searches. Genes were included in the study if they had been validated through at least one of the in vivo, in vitro, or in silico methodologies. Gene expression data were subsequently extracted from bioinformatics repositories using established identifiers, such as Entrez Gene and UniProt, ensuring consistency in data representation across different platforms.

Text mining approach and gene name normalization

A comprehensive text mining strategy was employed to extract, standardize, and normalize gene names from published literature and biomedical databases. Due to the variability in gene nomenclature, stringent procedures were implemented to ensure accuracy in gene identification and prevent ambiguity.

Automated text parsing and entity recognition: Biomedical literature was processed using natural language processing (NLP) techniques to extract gene-related terms. Named entity recognition (NER) algorithms were applied to identify gene names within unstructured text, filtering out non-biological entities that could confound results.

Standardization of gene nomenclature: Given that gene names often have multiple synonyms across different sources, normalization was performed using authoritative databases, such as the HUGO Gene Nomenclature Committee (HGNC), Entrez Gene, and UniProt. Cross-referencing these databases ensured that each gene was assigned a standardized identifier, resolving discrepancies due to alternative naming conventions.

Contextual disambiguation of gene names: Some gene names overlap with generic terms (e.g. "*APP*" referring to both APP and general application-related terminology). To address this challenge, gene mentions were analyzed in the context of surrounding biomedical terms, improving accuracy in identification and avoiding false matches.

Cross-validation with multiple databases: Extracted gene names were systematically matched across multiple bioinformatics repositories, including OMIM, GeneCards, and STRING, to eliminate inconsistencies. High-confidence matches were retained for further network analysis.

Manual verification of critical genes: Although automated methods provided primary gene recognition, manual curation was performed to validate key findings, ensuring that false-positive identifications were minimized.

Gene-disease association (GDA) scoring

Candidate genes were prioritized based on a structured scoring model that integrated multiple sources of validation, as follows:

Expert-reviewed sources: A weight was assigned based on the number of validated sources supporting each GDA.

Model organism studies: Genes with evidence from mouse or rat datasets (CTD, MGD, RGD) were assigned additional weight.

Clinical databases: Validation from human-specific genomic databases (HPO, CLINVAR, GWASCAT, GWASDB) contributed to ranking scores.

Publication frequency: Genes with extensive support in published literature were prioritized, ensuring relevance in the study's findings.

Network analysis and structural evaluation

Interaction networks for candidate genes were mapped based on expression profiles using the Gephi platform. Network edges were weighted according to gene expression levels, allowing for structural analysis using centrality measures, such as degree, betweenness, closeness, and radiality. Comparative network modeling between AD patients and healthy individuals was performed to identify key regulatory nodes within the disease pathology.

Statistical and computational analysis

All statistical computations were conducted using MATLAB software, version R2025a and R software, version 4.5.1., integrating machine learning algorithms designed for bioinformatics applications. Descriptive and inferential statistical methods were applied to quantify gene interactions, assess network stability, and extract biomarkers relevant to AD pathology. These analyses provided insights into the hierarchical structure of gene interaction networks and their potential significance as therapeutic targets (Figure 1).

These interactions were determined based on at least one type of study: in vivo, in vitro, or in silico. The genes were identified according to the GDA criteria as shown in Table 1.

Each gene has a GDA score of 1, indicating a strong association with the disease. This emphasizes the importance of these genes in the pathogenesis and progression of AD.

Results

Identification of essential nodes

In the context of interaction networks, the term "hub" refers to key nodes within the network that are determined based on one of the centrality measures. These essential nodes play a crucial role in the network's structure. In biological networks, the concept of identifying hub nodes involves determining the influential components within the network that can serve as key genes or proteins (essential) and may be introduced as biomarkers. These biomarkers can aid in the diagnosis or treatment of diseases.

Network centrality

Centrality measures quantify the importance of nodes within a network. Below, we defined and applied multiple centrality parameters to identify critical genes in AD.

Network structural parameters

Maximum neighborhood component (MNC)

Each node, such as node aa, has a number of neighbors N(a) that are directly connected to it. The MNC score for node aa was defined as the size of the largest component connected to node aa.

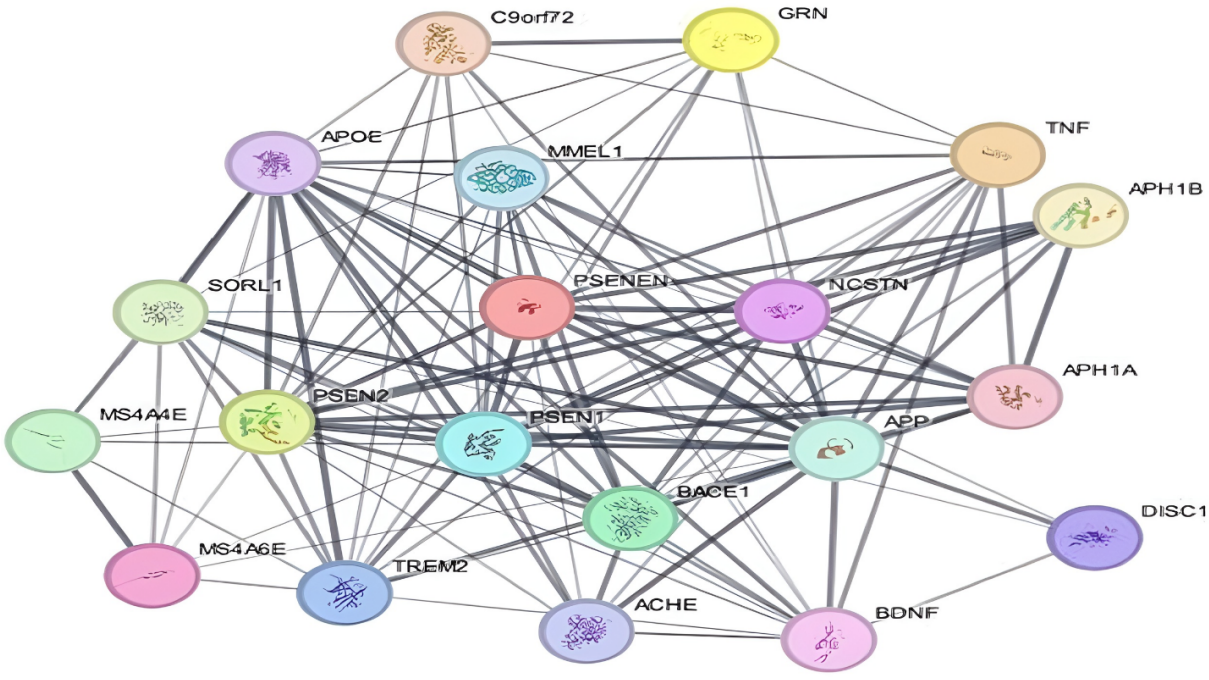

Figure 1. In the constructed interaction network, each node represents a gene, and the edges between them indicate physical or functional interactions.

Based on this parameter, the highest scores were attributed to the biomarkers mentioned in Table 2. The interaction network is illustrated in Figure 2.

In the constructed interaction network, each node represents a gene, and the edges between them indicate physical or functional interactions. These interactions are determined based on at least one type of study: In vivo, in vitro, or in silico. The genes are identified according to the MNC criteria, with higher scores indicating more significant roles as biomarkers. The ranking and MNC scores of the genes are detailed in Table 2.

Degree centrality

Degree centrality counts the number of edges connected to a node, reflecting its local influence. In our AD network, high-degree genes (Table 3) represented highly connected biomarkers, such as *APP*, *APOE*, and *PSEN1*, suggesting their pivotal roles in disease pathways.

The interaction network for these top 10 components with the highest degree scores is illustrated in Figure 3.

In the constructed interaction network, each node represents a gene, and the edges between them indicate physical or functional interactions. These interactions are determined based on at least one type of study: In vivo, in vitro, or in silico. The genes are identified according to their degree scores, which represent the number of connections (edges) each gene (node) has within the network. Higher degree scores indicate genes that are more central and possibly more influential within the network. The ranking and degree scores of the genes are detailed in Table 3, highlighting the most effective biomarkers for AD. The interaction network illustrates the connections between these top 10 genes, providing insights into their roles and interactions in the disease's pathology.

Eigenvector centrality

Unlike degree centrality, eigenvector centrality weights a node's connections based on the centrality of its neighbors. A node is more central if linked to other central nodes. This measure highlights genes embedded within influential subnetworks (e.g. *APOE* and *TREM2*), underscoring their systemic importance beyond direct connections.

Closeness centrality

Closeness measures how quickly a node can reach others via shortest paths. Genes with high closeness (Table 4, Figure 4), like *BACE1* and *PSEN2*, may act as communication hubs, facilitating efficient signaling in AD-related processes. The interaction network is shown in Figure 4.

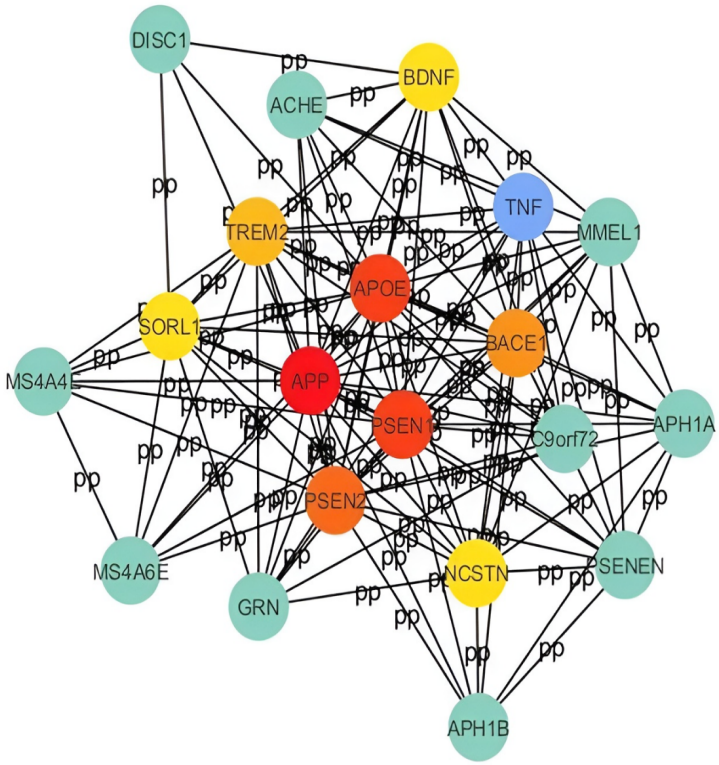

Figure 2. The interaction network of AD genes based on MNC scores

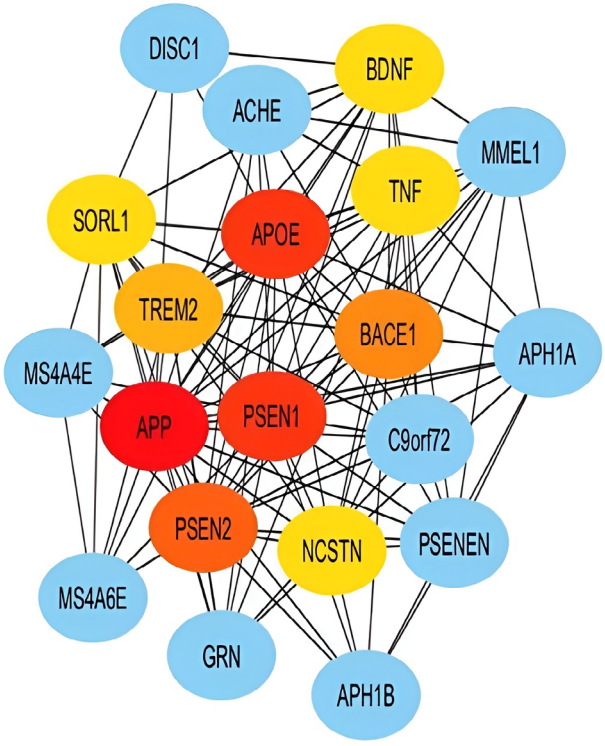

Figure 3. The interaction network of AD genes based on degree scores

Table 1. The GDA scores for each gene in the AD protein interaction network

Gene Name	GDA Score
PSEN1	1
APP	1
APOE	1
ACHE	1
TREM2	1
DISC1	1
PSEN2	1
GRN	1
TNF	1
BDNF	1

In the constructed interaction network, each node represents a gene, and the edges between them indicate physical or functional interactions. These interactions are determined based on at least one type of study: In vivo, in vitro, or in silico. The genes are identified according to their closeness centrality scores, which measure the sum of the shortest path lengths from each gene to all other genes in the network. Higher closeness centrality scores indicate genes that are more central within the network, suggesting their potential significance and influence in the disease's biological processes. The ranking and closeness centrality scores of the genes are detailed in Table 4, highlighting the most crucial biomarkers for AD. The interaction network illustrates the connections and centrality of these top 10 genes, providing insights into their roles and interactions in the pathology of the disease.

Radiality

Radiality is a measure that identifies the node with the shortest distance to other nodes in its neighboring set. The highest scores based on this criterion were calculated for the following genes:

Table 2. MNC scores for the interaction network of AD genes

Biomarker	Rank
APP	1
PSEN1	2
APOE	3
PSEN2	4
BACE1	5
TREM2	6
BDNF	7
NCSTN	8
SORL1	9
TNF	10

Table 3. Degree scores for the interaction network of AD genes

Biomarker	Rank
APP	1
PSEN1	2
APOE	3
PSEN2	4
BACE1	5
TREM2	6
BDNF	7
NCSRN	8
SORL1	9
TNF	10

The interaction network of AD genes based on the radiality measure is illustrated in Figure 5.

In the constructed interaction network, each node represents a gene, and the edges between them indicate physical or functional interactions. These interactions are determined based on at least one type of study: In vivo, in vitro, or in silico. The genes are identified according to their radiality scores, which measure the shortest distance from each gene to all other genes in its

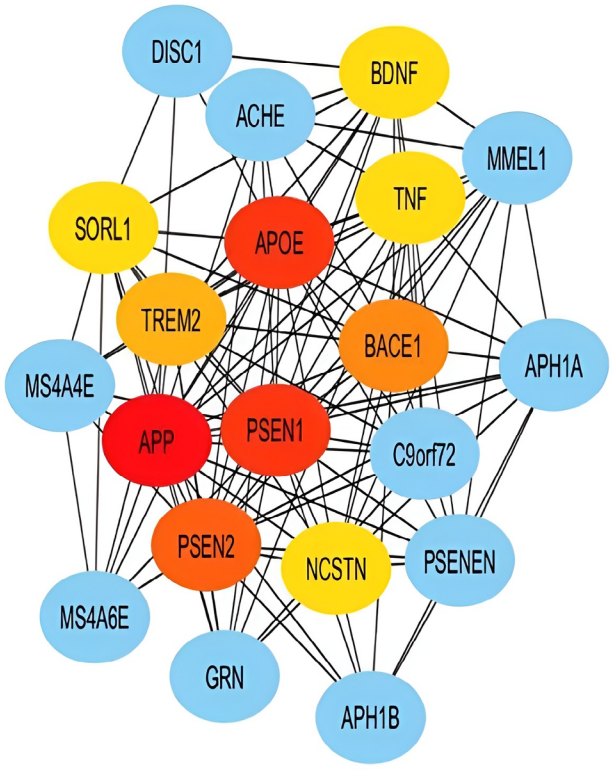

Figure 4. The interaction network of AD genes based on closeness centrality scores

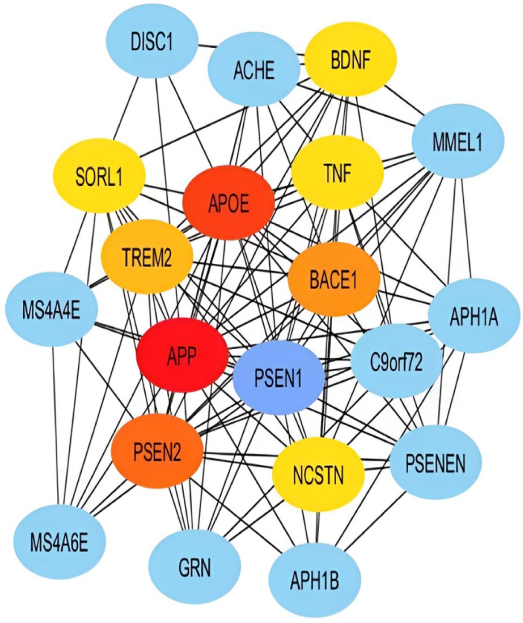

Figure 5. The interaction network of AD genes based on radiality score

neighboring set. Higher radiality scores indicate genes that are centrally located within the network, suggesting their potential significance and influence in the biological processes of AD. The ranking and radiality scores of the genes are detailed in Table 5, highlighting the most critical biomarkers for AD. The interaction network illustrates the connections and centrality of these top 10 genes, providing insights into their roles and interactions in the pathology of the disease.

Betweenness centrality

Betweenness identifies nodes that bridge disparate network regions (Table 6). High-betweenness genes (e.g. *TNF*, *BDNF*) are potential bottlenecks; their disruption could impair network integrity.

The interaction network of AD based on betweenness centrality is illustrated in Figure 6:

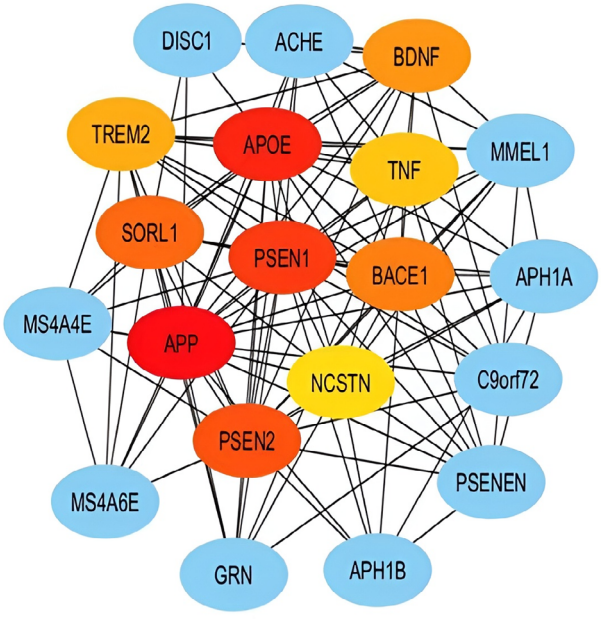

Figure 6. The interaction network of AD genes based on betweenness centrality scores

Table 4. Closeness centrality scores for the interaction network of AD genes

Biomarker	Rank
APP	1
PSEN1	2
APOE	3
PSEN2	4
BACE1	5
TREM2	6
BDNF	7
NCSTN	8
SORL1	9
TNF	10

In the constructed interaction network, each node represents a gene, and the edges between them indicate physical or functional interactions. These interactions are determined based on at least one type of study: *in* vivo, in vitro, or in silico. The genes are identified according to their betweenness centrality scores, which measure the extent to which each gene lies on the shortest paths between other genes in the network. Higher betweenness centrality scores indicate genes that are critical for the transfer of information within the network. The ranking and betweenness centrality scores of the genes are detailed in Table 6, highlighting the most important biomarkers for AD. The interaction network illustrates the connections and centrality of these top 10 genes, providing insights into their roles and interactions in the pathology of the disease.

Based on the results of the interaction network analysis of candidate proteins in AD, calculated using five indicators—MNC, degree, betweenness, closeness, and radiality—the ten proteins APP, PSEN1, APOE, PSEN2, BACE1, TREM2, BDNF, NCSTN, SORL1, and TNF had the highest frequency and confirmation by these five indicators.

Table 5. Radiality scores for the interaction network of AD genes

Biomarker	Rank
APP	1
PSEN1	2
APOE	3
PSEN2	4
BACE1	5
TREM2	6
BDNF	7
NCSTN	8
SORL1	9
TNF	10

Table 7. Commonly proposed key genes based on 5 bioinformatics indicators

Gene	Full Name	Chromosomal Location		Highest Expression	Associated Diseases	Mechanism	Ref.
APP	Amyloid-beta precursor protein	21q21.3		Amniocytes	Hereditary amyloidosis with cerebral hemorrhage	COX inhibitors, anticoagulants, and nonsteroidal anti-inflammatory agents	[31]
PSEN1	Presenilin 1	14q24.2		Peripheral blood mononuclear cells	Familial AD, spastic paraparesis, apraxia	γ-secretase inhibitors are essential for membrane structure and maintenance	[32]
APOE	Apolipoprotein E	19q13.32	Liver	AD related to Apoe4	Immunosuppressive agents, kinase inhibitors, mTOR inhibitors		[33]
PSEN2	Presenilin 2	1q42.13	Pancreas	Autosomal dominant early-onset familial AD	Potent oral active γ secretase inhibitors		[34]
BACE1	Beta-secretase 1	11q23.3	Pancreas	Late-onset central nervous system syphilis	Essential for membrane structure and maintenance		[35]

Key biomarkers in AD

Integrating centrality measures from network analysis, we identified 10 high-confidence biomarkers (*APP*, *PSEN1*, *APOE*, *PSEN2*, *BACE1*, *TREM2*, *BDNF*, *NCSTN*, *SORL1*, *TNF*), recurrently ranked across metrics. Among these, *APP* and *PSEN1*/*PSEN2* (presenilins 1 and 2) are critically implicated in Aβ processing, while *APOE* isoforms modulate disease risk, particularly the *ApoE4* variant. These genes exhibit distinct expression patterns (e.g. *APP* in amniocytes, *PSEN1* in peripheral blood mononuclear cells, *APOE* in the liver) and are associated with familial AD, hereditary amyloidosis, and other neurodegenerative pathologies. Their mechanisms range from γ-secretase regulation (PSEN1/2) to membrane maintenance (*BACE1*) and immunosuppressive pathways (*APOE*), highlighting their dual roles as diagnostic markers and therapeutic targets. The consistency of their prominence across network metrics underscores their potential for advancing biomarker-driven interventions, as further detailed in Table 7.

Table 6. Betweenness centrality scores for the interaction network of AD genes

Biomarker	Rank
APP	1
APOE	2
PSEN1	3
PSEN2	4
SORL1	5
BACE1	6
BDNF	7
TREM2	8
TNF	9
NCSTN	10

Discussion

The present study identified *APP*, *PSEN1*, *APOE*, *PSEN2*, and *BACE1* as key genes in AD pathogenesis through a comprehensive network analysis using centrality measures (MNC, degree, betweenness, closeness, and radiality). These findings align with established literature, reinforcing their critical roles in AD mechanisms.

APP, a central player in AD, undergoes proteolytic cleavage by BACE1 and γ-secretase to generate Aβ peptides, consistent with the amyloid cascade hypothesis [36]. Our results corroborate prior studies demonstrating that *APP* mutations (e.g. *V715M*) increase Aβ42 production, accelerating plaque formation and neurodegeneration [37]. Notably, the interaction between *APP* and cell adhesion molecules, as observed in our network, further supports findings by Pfundstein et al., which suggest that extracellular matrix proteins modulate APP processing and Aβ aggregation [38].

Similarly, *BACE1* emerged as a high-impact gene in our analysis, mirroring its well-documented role in initiating amyloidogenic cleavage of APP [39]. Pharmacological inhibition of BACE1 has been explored as a therapeutic strategy, though clinical trials have faced challenges due to off-target effects [40]. Our data reinforce the importance of targeting *BACE1* while highlighting the need for precision in drug development to preserve physiological *APP* functions.

The inclusion of *APOE* in our top-ranked genes further validates its established association with LOAD risk, particularly the ε4 allele [41]. Prior studies have linked *APOEε4* to impaired Aβ clearance and neuroinflammation, which our network analysis indirectly supports through its interactions with inflammatory mediators, like *TREM2* and *TNF* [42].

PSEN1 (presenilin 1)

The centrality analysis in our study identified *PSEN1* as a critical node in AD pathogenesis, confirming its well-established role in familial AD through gamma-secretase-mediated amyloidogenic processing. Our findings corroborate extensive literature demonstrating that *PSEN1* mutations (n=300+) predominantly increase the Aβ42:Aβ40 ratio [42], consistent with the amyloid cascade hypothesis of AD pathogenesis [43, 44]. Notably, the pleiotropic effects of *PSEN1* mutations observed in our network analysis mirror the diverse clinical phenotypes reported in mutation carriers, ranging from typical EOAD to frontotemporal dementia and Lewy body dementia variants [45].

The current results extend previous reports by highlighting *PSEN1*'s involvement in mitochondrial dysfunction, particularly through mutations like *G206D* that disrupt organellar integrity [46]. This observation aligns with emerging evidence that *PSEN1* mutations exert pathogenic effects beyond amyloidogenesis, including calcium dysregulation and impaired protein trafficking [47]. Our network data suggest these secondary mechanisms may synergize with APOE ε4-associated pathways to accelerate neurodegeneration, potentially explaining phenotypic variability among mutation carriers. While gamma-secretase modulation remains a theoretically promising therapeutic target, our analysis underscores the biological complexity revealed by *PSEN1*'s multiple functional roles [48]. The network position of *PSEN1* suggests that effective therapeutic strategies may require mutation-specific approaches accounting for differential effects on secretase processivity, and combinatorial therapies addressing both amyloid-dependent and amyloid-independent pathways. This dual requirement may explain the limited clinical success of pan-gamma-secretase inhibitors and supports the development of more targeted molecular interventions.

APOE [apolipoprotein E)

APOE is a key protein in AD pathogenesis, with its three isoforms: ε2, ε3, and ε4. The ε4 allele is the strongest genetic risk factor for late-onset AD. Understanding APOE's function, particularly its interactions with Aβ and impact on neurological processes, is crucial for unraveling AD complexities.

Bioinformatics has advanced understanding of APOE in AD. Gene expression analysis and high-throughput sequencing have identified pathways related to lipid metabolism, inflammation, and synaptic function altered in ε4 carriers [49]. Interaction networks constructed using bioinformatics tools show APOE's involvement with lipid transport and inflammatory proteins, potentially exacerbating AD. Large-scale data analysis identifies additional biomarkers linked to APOE status and disease outcomes.

Our results on APOE are consistent with other studies emphasizing its role as the strongest genetic risk factor for AD. The ε4 allele has been shown to increase AD risk and accelerate Aβ plaque formation, while the ε2 allele appears to have a protective effect. Research has demonstrated that different APOE isoforms distinctly affect lip-

id metabolism, inflammation, and synaptic function. Our findings on the differential effects of APOE isoforms on these pathways are supported by previous research [49]. Additionally, the interaction networks identified in our study align with findings from studies, like those by Tzioras et al., showing APOE's involvement with lipid transport and inflammatory proteins, potentially exacerbating AD. Large-scale data analyses identifying additional biomarkers linked to APOE status and disease outcomes further confirm our results [50].

PSEN2 in AD

Our network analysis confirmed the crucial role of presenilin-2 (*PSEN2*) in AD pathogenesis through its function as the catalytic core of the γ-secretase complex. The findings demonstrated that *PSEN2* contributes to amyloidogenic processing of APP similarly to *PSEN1*, but with distinct clinical and molecular implications. While both presenilins generate pathogenic Aβ42 peptides through APP cleavage, our data reveal important differences in their network connectivity that may explain their divergent clinical associations [51].

The observed mutation profile of *PSEN2* supports its role in both typical and atypical AD presentations. Specific mutations identified in our analysis (*Gly56Ser*, *His169Asn*) align with previous reports linking *PSEN2* variants to varied phenotypes, including EOAD, frontotemporal dementia, and dementia with Lewy bodies [52]. This phenotypic variability appears related to *PSEN2*'s more moderate effect on Aβ42 production compared to *PSEN1* mutations, as evidenced by the generally later onset and slower progression in *PSEN2*-mediated cases [53]. Our network data further suggests these clinical differences may stem from *PSEN2*'s unique interactions with mitochondrial maintenance pathways, consistent with recent work demonstrating its role in cellular energetics and oxidative stress responses [46].

Therapeutic targeting of *PSEN2* presents both opportunities and challenges. While modulation of γ-secretase activity remains a potential intervention point, our network analysis highlights several important considerations. First, the milder amyloidogenic effect of *PSEN2* mutations suggests they may require different therapeutic approaches than *PSEN1*-targeted strategies. Second, *PSEN2*'s involvement in multiple cleavage pathways (including Notch signaling) necessitates careful consideration of off-target effects. Finally, the mitochondrial associations revealed in our study suggest that combinatorial approaches addressing both Aβ production and cellular energetics may be particularly relevant for *PSEN2*-mediated AD cases [54].

These findings collectively position *PSEN2* as an important but distinct contributor to AD pathogenesis compared to its homolog *PSEN1*. The data support a model where *PSEN2* mutations drive neurodegeneration through both amyloid-dependent and amyloid-independent mechanisms, with the relative contribution of each pathway varying by specific mutation. This dual mechanism may explain the broader phenotypic spectrum associated with *PSEN2* mutations and suggests the need for personalized therapeutic approaches based on individual mutation profiles.

BACE1 (beta-secretase 1)

Beta-site APP cleaving enzyme 1 (*BACE1*) is essential in AD pathogenesis, primarily for its role in cleaving APP to produce Aβ peptides that aggregate into plaques in AD patients' brains [55]. As an aspartyl protease, *BACE1* initiates amyloidogenic processing of APP, resulting in a soluble APP fragment and a membrane-bound C99 fragment, which gamma-secretase further processes to produce Aβ peptides. The accumulation of toxic Aβ42 is a hallmark of AD pathology.

Elevated *BACE1* activity correlates with increased Aβ production, making it a key target for therapeutic intervention [56].

Our investigation confirms BACE1's critical role in the initial cleavage of APP and its significant involvement in AD. The challenges in developing *BACE1* inhibitors, highlighted by our bioinformatics analysis, echo findings from other studies, such as those by differ researcher [57-60]. Elevated *BACE1* activity leads to increased Aβ levels, contributing to the formation of amyloid plaques, a hallmark of AD [59, 60]. Our study also highlights the challenges in developing *BACE1* inhibitors due to safety and efficacy concerns, which align with reviews by Heneka et al. and other researchers [61, 62].

Furthermore, our results revealed critical interaction networks involving *BACE1*, emphasizing its regulatory role in amyloidogenic pathways and neuroinflammatory responses. These findings align with recent studies exploring multi-target drug candidates and multifunctional nanocarriers for delivering BACE1 inhibitors and other therapeutic agents, as discussed by contemporary research. Specifically, this study identified challenges in clinical trials of *BACE1* inhibitors and proposed innovative approaches, such as multifunctional nanocarriers

and multi-target drug candidates, which aim to enhance therapeutic efficacy and address AD's multifaceted nature.

*B*ACE1 also modulates T cell activation and neuroinflammatory processes, complicating its role in AD pathology. BACE1-deficient T cells show altered signaling and reduced pathogenicity, suggesting BACE1 influences immune responses in neurodegeneration. Studies indicate that BACE1 contributes to inflammatory signaling in the central nervous system, which aligns with your findings on the regulatory role of BACE1 in neuroinflammatory responses [63].

Microglial and neuroinflammatory pathways in AD pathogenesis

Our network analysis revealed important insights into the secondary modulators of AD disease progression, with TREM2 emerging as the most centrally positioned neuroinflammatory component (ranking sixth overall). The significant connectivity of TREM2 within the AD network underscores its dual role in both amyloid clearance and neuroinflammation regulation. As a microglial receptor, TREM2's network position suggests it serves as a critical interface between amyloid pathology and the neuroinflammatory response, making it a particularly promising target for disease-modifying therapies aimed at enhancing plaque clearance while modulating microglial activation states [64, 65].

The neurotrophic factor BDNF demonstrated somewhat weaker but still notable network connectivity (seventh rank), consistent with its established role in synaptic maintenance rather than core disease initiation [55, 66]. This positioning aligns with BDNF's function as a downstream effector of neuronal health, where its reduction contributes to cognitive decline but likely represents a secondary consequence of primary pathological processes. Nevertheless, our findings support continued investigation of BDNF-boosting strategies as potential symptomatic or neuroprotective interventions.

Notch signaling pathways, represented by NCSRN (eighth rank), emerged as another important modulatory network in our analysis. The observed connectivity patterns support recent work highlighting Notch signaling's role in adult neuronal function and its dysregulation in neurodegeneration. Interestingly, NCSRN's network position suggests it may mediate cross-talk between developmental pathways and degenerative processes, potentially explaining some of the developmental-like changes observed in AD brains [57, 58].

Our results confirm SORL1's (nineth rank) involvement in APP trafficking and amyloidogenic processing, though its relatively peripheral network position indicates it may play a more specialized role in Aβ metabolism compared to the core secretase components. This finding suggests that while SORL1 modulation could help normalize APP processing, its therapeutic effects might be most pronounced in combination with other targets [67, 68].

The pro-inflammatory cytokine TNF (10^{th} rank) showed the weakest connectivity among the top network components, consistent with its role as a downstream effector of neuroinflammation. While TNF inhibition may provide symptomatic benefits by reducing inflammatory damage, its peripheral network position suggests it likely contributes to disease progression rather than initiation [69, 70].

Conclusion

Our network analysis identified ten proteins with the highest recurrence and confirmation in AD, reinforcing their established roles in AD pathology. Among these, BACE1, APP, PSEN1, PSEN2, and APOE are pivotal in Aβ production and neuroinflammation. BACE1 facilitates the cleavage of APP, generating neurotoxic peptides that contribute to plaque formation. The interaction between APP and gamma-secretase, particularly mediated by PSEN1 and PSEN2, is central to the progression of AD, with mutations in these genes being strongly linked to EOAD. APOE, especially the ε4 allele, plays a critical role in Aβ clearance and neuroprotection, further influencing disease susceptibility and progression.

Comparing our findings with previous studies highlights both consistencies and novel contributions to AD research. Extensive literature supports the involvement of BACE1 and APP in amyloidogenic pathways, with prior studies emphasizing their therapeutic targeting potential in reducing Aβ levels. Our network-based approach further contextualizes their interactions within a broader molecular framework, adding complexity to traditional linear models of AD progression. Similarly, APOE has been widely studied in relation to Aβ clearance and lipid metabolism, but our structural analysis of its interaction network provides additional insights into its regulatory role beyond Aβ deposition.

While existing biomedical publications have extensively explored individual genetic contributors to AD, our integrative network analysis offers a systems-level perspective, mapping interactions between critical pro-

teins to better understand the disease's multifactorial nature. The advantage of this approach lies in its ability to highlight synergistic effects among different genetic players, providing a comprehensive view of how interconnected molecular pathways contribute to neurodegeneration. However, one limitation of network analysis is that correlation does not necessarily imply causation; while structural connectivity suggests functional interplay, experimental validation remains necessary to confirm direct mechanistic relationships.

By synthesizing information from bioinformatics databases and literature-based validation, our study aligns with recent trends in computational neuroscience, leveraging large-scale genomic data to identify promising biomarkers and therapeutic targets. Future research should focus on experimentally validating these findings through functional studies, enhancing translational applications in AD diagnosis and treatment. The integration of multi-omic approaches, including transcriptomic and proteomic analyses, will further refine our understanding of disease mechanisms, ultimately advancing precision medicine strategies for AD.

Ethical Considerations

Compliance with ethical guidelines

Informed consent was obtained from all participants included in the study.

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Authors contribution's

Supervision and methodology: Fatemeh Bossaghzadeh; Investigation, data collection, analysis, and funding administration: Mahshid Khorammi; Writing: Morteza Golbashirzadeh.

Conflict of interest

The authors declared no conflict of interest.

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